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Rare primary testicular lymphoma: a single-center analysis

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Abstract

Introduction: Primary testicular lymphoma (PTL) is a rare disease, accounting for <5% of all testicular malignancies and 1–2% of non-Hodgkin lymphoma cases. Diffuse large B-cell lymphoma (DLBCL) is the most common histological diagnosis. The literature data concerning PTL is scarce and based mainly on small series or retrospective studies.

Methods and results: In this paper, we present six patients with DLBCL-PTL who were treated in the Department of Hematology and Bone Marrow Transplantation at Poznan University of Medical Science, Poland between 2006 and 2022. All the patients obtained complete remission (CR) after six cycles of R-CHOP-21 (cyclophosphamide, doxorubicin, vincristine and rituximab on day 1, and prednisolone on days 1–5, administered every 21 days for a total of eight cycles) as immunochemotherapy. Five of them additionally received prophylaxis of central nervous system involvement with intrathecal methotrexate/arabinoside cytosine. One patient received scrotal radiotherapy, and in another one radiotherapy is planned. Relapse was confirmed in one patient after 72 months in the contralateral testis, and the patient was successfully retreated. After a median follow-up of 146 (range 5–196) months, all patients remain alive and in CR.

Conclusion: Despite all interpretative limitations, the current standard DLBCL-PTL therapy seems to be six courses of CHOP-R-21 combined with intrathecal metothrexate and scrotal irradiation.

Key words: primary testicular lymphoma, extranodal lymphoma

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Introduction

Primary testicular lymphoma (PTL) is an aggressive form of non-Hodgkin lymphoma (NHL) representing c.1–2% of all NHLs and c.1–7% of testicular malignancies [1]. It is worth noting that PTLs comprise the most common testicular tumors in men with a median age of 66–68 years. It is estimated that the annual incidence amounts to 0.09–0.26 per 100,000 population [1, 2]. Inguinal orchiectomy is recommended when PTL is suspected. A proper panel of immunohistochemical staining and an evaluation by an experienced pathologist is crucial for appropriate diagnosis, because PTL is rare and can be difficult to distinguish from seminoma in some cases [3].

The vast majority of PTLs exhibit the histology of diffuse large B-cell lymphoma (DLBCL; 80–90%) [4]. The 5th edition of the 'World Health Organization Classification of Hematolymphoid Tumors: Lymphoid Neoplasms' included PTL-DLCBLs in a category of primary large B-cell lymphomas of immune-privileged sites in addition to the primary

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central nervous system DLBCL and primary large B-cell lymphoma of the vitreoretina [5]. Nevertheless, isolated cases of other histological subtypes such as follicular lymphoma, marginal zone lymphoma, Burkitt's lymphoma, anaplastic large cell lymphoma, lymphoblastic lymphoma, mantle cell lymphoma, natural killer (NK)/T lymphoma, and peripheral T-cell lymphoma have also been found [6–12]. DLBCL-PTL differs from nodal DLBCL in some aspects including the cell of origin, genetics and pathophysiology. PTLs, similarly to the other primary extranodal DLBCLs, are mainly of activated B-cell-like origin (ABC). PTL usually demonstrates with a non-tender, firm mass of a medium size of 6 cm, difficult to separate from the involved testis [13]. The right testis is as frequently involved as the left, while bilateral testicular involvement is rare, accounting for only c.6% of cases [1]. Recommended staging and response assessment procedures are no different from other forms of NHL, and include computed tomography (CT) or positron emission tomography–computed tomography (PET-CT) for routine staging of ^{18}F-fluoro-deoxy-glucose (FDG)-avid lymphomas which include almost all histologies [14].

Moreover, PTL may be associated with central nervous system (CNS) involvement, and therefore lumbar puncture and magnetic resonance imaging (MRI) are mandatory at diagnosis. According to the Lugano classification, extranodal lymphomas can be diagnosed only in stage I, when a single extranodal lesion is diagnosed or in stage II when nodal extent with limited contiguous extranodal involvement is observed. Stages III and IV are not applicable for extranodal lymphomas, because they are the equivalent of advanced disease [14]. Patients with isolated bilateral involvement of the testes have a prognosis similar to that of patients with stage I/II disease, and therefore they should be considered as stage I [15]. In PTLs, most patients experience a relapse in numerous regions of their body as long as 10–15 years after the initial diagnosis. Relapses are often observed in sanctuary sites such as the contralateral testis and CNS [2, 16–19]. The other sites of relapse can include skin, Waldeyer's ring, lung, pleura, adrenal glands, kidney, liver, and bone marrow, and even eye and heart [2, 16–20]. PTL cases are mainly reported as small series or small retrospective studies. To the best of our knowledge, there have only been three PTL prospective studies [21–23].

Therefore, to date there is a lack of standardized treatment regimen guidelines. In this paper, we summarize our center's experience of PTL and discuss that in the context of the literature data.

Methods and results

Among the lymphoma patients treated in the Department of Hematology and Bone Marrow Transplantation at Poznan University of Medical Science Poland between 2006 and 2022, we identified six patients with truly PTL lymphoma. Five testicular lymphoma patients with concomitant other sites involvement were excluded from the analysis. The median age of PTL patients was 62 years (range: 54–74), and all patients were in a good performance status according to the Eastern Cooperative Oncology Group (ECOG) 0–1. In all of them, DLBCL was diagnosed. Based on the Hans algorithm, it was possible to confirm the cell of origin subtype in three of the patients. All patients were initially treated with inguinal orchidectomy. PTL was diagnosed after exclusion of other sites involvement, based on CT scans or PET-CT, lumbar puncture, and bone marrow examination. None of the patients presented with B symptoms. All patients were treated with six courses of chemotherapy: in four of them, CHOP-R-21 (cyclophosphamide, doxorubicin, vincristine and rituximab on day 1, and prednisolone on days 1–5, administered every 21 days for a total of eight cycles) was given in all courses of treatment; in two of them, 2-3 initial courses of CHOP-21 was not combined with rituximab. Additionally, five of them received primary CNS involvement prophylaxis including repeated doses of intrathecal (i.t.) methotrexate (MTX) 15 mg and/or arabinoside cytosine 40 mg.

After the treatment, all patientsachieved complete remission (CR) based on CT or PET-CT. In one patient, scrotal radiotherapy 30 Gy was performed, and in another one radiotherapy (RT) is planned. Unfortunately, in one patient who did not receive RT, relapse in the contralateral testis was confirmed after 72 months. This patient underwent orchidectomy combined with CHOP-R modo Travade/COP-R immunotherapy and liposomal arabinoside cytosine i.t. prophylaxis all with subsequent the second CR. After a median follow-up of 146 (5–196) months, all patients remain under observation without signs of active disease. Detailed patient characteristics are set out in Table I.

Discussion

Clinical characteristics of, and clinical course in, our patients are consistent with literature data. Most literature analyses are difficult to interpret because treatment protocols differ. Moreover, the studies often include patients presenting with testicular involvement being a part of disseminated disease, which nowadays cannot be regarded as truly PTL. In the literature, the proportion of ABC subtypes in PTLs ranges between 60% and 96% and is dependent on the diagnostic method, with a higher incidence when using gene expression profiling than when using immunohistochemistry [24–26]. Additionally, in PTL *TP53* mutations are unlikely, but a high proportion of patients show active STAT signaling, and expression of nuclear p50 suggesting the activity nuclear factor κB (NF-κB) signaling pathway is observed [27]. It must be underscored that there is a similarity of PTLs to primary central nervous system lymphomas (PCNLs), in that both present with genomic

Table I. Patient characteristics, treatments and outcomes

Patient number	Age	Laterality	IPI	Stage	Chemotherapy	Intrathecal prophylaxis	Response	Radiotherapy	Relapse	Alive	Time of follow-up (months)
1	64	Left	1	IE	6 × CHOP-R	3 × MTX + Ara-C	CR	No	Yes (contralateral testis)	Yes	143
2	58	Left	1	IE	3 × CHOP 3 × CHOP-R	No	CR	No	No	Yes	156
3	54	Left	1	IIE	6 × CHOP-R	3 × MTX	CR	No	No	Yes	149
4	60	Right	ND	IE	2 × CHOP 4 × CHOP-R	3 × MT	CR	No	No	Yes	196
5	66	Left	1	IE	6 × CHOP-R	2 × MTX	CR	Planned	No	Yes	5
6	74	Right	1	IE	6 × CHOP-R	3 × MTX	CR	Yes (30 Gy)	No	Yes	20

CHOP-R — cyclophosphamide 750 mg/m² intravenous (i.v.) on day 1, rituximab 375 mg/m² i.v. on day 1, doxorubicin 50 mg/m² i.v. on day 1, vincristine 2 mg (pts <70-years) or vincristine 1 mg (pts >70-years) i.v. on day 1, prednisone 100 mg per os daily, day 1–5; MTX — metothrexate; Ara-C — arabinoside cytosine; CR — complete remission; ND — no data

instability, and near-uniform, often biallelic, CDKN2A loss with rare *TP53* mutations [28]. PCNSLs and PTLs also utilize multiple genetic mechanisms to target key genes and pathways and exhibit near-uniform oncogenic Toll-like receptor signaling due to *MYD88* mutation and/or NFKBIZ amplification, frequent concurrent B-cell receptor pathway activation, and BCL6 deregulation. Interestingly, PCNSLs and PTLs have frequent 9p24.1/PD-L1/PD-L2 CNAs and additional translocations of these loci, structural bases of immune evasion that are shared with primary mediastinal large B-cell lymphoma.

In PTL, high *MYD88* expression is typically observed and *MYD88L265P* mutation is found in c.70% of patients [29, 30]. The morphology of testicular lymphoma is not pathognomonic in ultrasound, presenting with unifocal, multifocal or diffuse hypoechogenic areas and can be difficult to distinguish from an inflammatory process [31]. Magnetic resonance imaging (MRI) is a more sensitive technique which allows simultaneous evaluation of both testes, paratesticular spaces, and spermatic cord. In MRI, typical PTL findings include T2-hypointensity and strong heterogeneous gadolinium enhancement [32]. Similarly to the other extranodal lymphomas, in PTL the prognostic utility of International Prognostic Index (IPI) and its components seems to be limited, because they are surrogate markers of a high tumor burden and disseminated disease. Indeed, all our patients had IPI 1. In the available literature, the following biological, clinical, and laboratory factors were considered as adverse prognostic factors: age >70 years, left testis involvement, a lack of surgery or RT [1], an infiltration of adjacent tissues including either spermatic cord or epididymis or scrotum, ECOG ≥2, and bulky disease (tumor mass >9 cm) [33], high lactate dehydrogenase (LDH) or high beta$_2$-microglubulin, B symptoms, tumor size >10 cm [2].

Orchidectomy is necessary for both diagnostic and therapeutic purposes, but the outcomes of patients treated with orchidectomy alone are poor. Additionally, treatment with surgery combined with RT but omitting immunochemotherapy is considered as an independent predictor of worse survival [1] and should be reserved only for PTL patients who are ineligible for systemic chemotherapy. Due to the rarity of PTL, no prospective randomized trial has been performed so far.

The results of selected studies are set out in Table II. With regard to the PTL treatment strategies, the time of treatment, the choice of the first line treatment, the role and type of CNS prophylaxis, and finally the impact of RT on patient outcome, have all been discussed in the literature. First, independent of the limited character of PTLs, the literature data suggests that PTL patients have a significantly better long-term outcome when treated with at least six cycles of chemotherapy compared to an abbreviated treatment schedule [2, 17]. MD Anderson Cancer Center analysis showed significant improvements on both progression-free survival (PFS) and overall survival (OS) over time, reflecting the refinement of treatment strategy. The authors reported 5-year OS of 15.4% and 5-year PFS of 15.4% in patients treated before 1977 predominantly with chemotherapy without doxorubicin, while patients treated in 1977–1999 with doxorubicin-based chemotherapy without rituximab had a 5-year OS and PFS of 56.3% and 51.7% respectively. Patients treated since 2000, mainly with R-CHOP, had a 5-year OS and PFS of 86.6% and 59.3%, respectively (p = 0.019 for OS and p = 0.138 for PFS). Additionally, the patients treated after 2,000 were more likely to receive i.t. prophylaxis [34]. Finally, a CHOP-21 regimen was the most widely used regimen for PTL prior to the introduction of rituximab, with 5-year OS ranging from 30% to 52% [34, 35]. Similarly to the other extranodal lymphomas, the impact of rituximab addition to the chemotherapy in PTL seems to be less important than in the nodal forms. However, some retrospective analyses have confirmed its benefit in terms of time to progression, OS, PFS or the risk of relapse [34,

36, 37]. In the literature data, the rates of CNS relapses are divergent ranged from 0 to 15% [2, 20]. CNS relapses are often detected up to 10 years after an initial presentation of PTL [2, 23, 24]. CNS relapse i.t. prophylaxis with MTX has been reported in many studies with differing MTX application doses [23, 34, 37]. Of the prospective clinical trials previously reported, two used intrathecal chemotherapy alone and reported CNS relapse rates of 6% [21, 22], while one used both intrathecal and systemic MTX. Given the fact that more relapses have a parenchymal pattern, and that the penetration of MTX into the brain may be limited, it seems to be rational to use high-dose systemic MTX for CNS prophylaxis. Aviles et al.'s prospective study with the use of 4 × MTX 6 g/m^2 intravenous (i.v.) every 28 days found mild hematological and nonhematological toxicity. After a median follow-up of 64.8 months,

Table II. Results of prospective and selected retrospective studies containing more than 50 patients presenting with testicular lymphoma

Authors, type of study	No of pts	Age	Stage I/IIE [%]	Chemotherapy	Radiotherapy	Rate of response	Relapses	Outcome
Vitolo et al., 2011 (IELSG-10 trial) [20]	53	54 (22–79)	100	6–8 CHOP-R-21 i.v. + 4 × MTX i.t.	30 Gy contralateral testis + 30–36 Gy regional LN	52 pts (98%) CR	9 pts (2 LN, 5 EN*, 3 CNS)	FU 65 mo 5-y PFS 74% 5-y OS 85%
Linassier et al., 2002 GOELAMS Study Group [21]	16	62 (29–73)	100	Age 18–60 y: VCAP i.v. Age 61–75 y: VECP--bleo i.v. MTX i.t. all	RT: inguinal, iliac and para--aortic	100% CR	LN 1 pt EN 3 pts (1 testis) CNS 1 pt	FU 73 mo ≤60-y DFS 66% OS 83% >60-y DFS 74% OS 56%
Aviles et al., 2009 [22]	38	52 (53–70)	100	COEP-R-14 CNS prophylaxis 4 × MTX 6 g/m^2 i.v. every 28 days	30 Gy to scrotum and contralateral testis (stage IE) or scrotum, contralateral testis, paraaortic iliac and pelvic lymph nodes (stage IIE)	86%	10 EN	FU 64.8 mo 5-y EFS 70% 5-y OS 66%
Gundrum et al., 2009 [1]	769	68 (21–98)	75	CHT ND	Surgery and RT 35.9% Surgery 59.3% RT 1.6%	ND	ND	Median OS 4.6-y DSS in: • 3-y 71.5% • 5-y 62.4% • 15-y 43%
Zucca et al., 2003 [2]	373	66 (19–91)	79	Systemic CHT 279 (75%) Aggressive regimens 255 (68%) CHOP or 2nd-line CHT 191 (51%) MACOP-B, proMACE/ /proMACE/3rd generation regimens 45 pts (12%) High-dose CHT and/or auto-SCT 19 pts (5%) Non-anthracycline-based regimen (CVP) or single alkylating agent 24 (6%) MTX i.t. 73 (20%) High-dose MTX i.v. 29 (8%)	RT 196 (53%) + CHT 145 (39%) RT — contralateral testis 133 (36%) Anthracycline--based CHT + + i.t. prophylaxis and scrotal irradiation 34 (9%)	ND	195 (52%) EN ± ND 140 (72%) including contralateral testis in 31 pts (16%)	Median OS: • 4.8-y/whole group • 5.8-y/pts in stage I/II 5-y PFS 48% 10-y OS 27% 5-y PFS 48% 10-y PFS 33% Median PFS of 4 years

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Table II (cont.). Results of prospective and selected retrospective studies containing more than 50 patients presenting with testicular lymphoma

Authors, type of study	No of pts	Age	Stage I/IIE [%]	Chemotherapy	Radiotherapy	Rate of response	Relapses	Outcome
Mazloom et al., 2010 [33]	75	64 (22–82)	62	Non-doxorubicin based CHT + RT 4 pts (6%) Doxorubicin based CHT alone (without rituximab) 15 pts (23%) Doxorubicin based CHT (without rituximab) + RT 8 pts (12%) Doxorubicin based CHT (without rituximab) + i.t. prophylaxis 3 pts (5%) Doxorubicin based CHT (without rituximab) + RT + i.t. prophylaxis 11 pts (17%) R-CHOP + RT 1 R-CHOP + i.t. prophylaxis 5 pts (8%)	RT alone 6 pts (9%)	CR 67% PR 2%	40 pts (57%) CNS 9 (23%) LN 8 pts (20%) Contralateral testis 5 (13%)	Pts after 2000 treated predominantly with R-CHOP + i.t. prophylaxis, and scrotal RT 5-y OS 86.6% 5-y PFS 59.3% Pts treated between 1977 and 1999 with doxorubicin based CHT without rituximab, not uniformly treated with i.t. prophylaxis 5-y OS 56.3% 5-y PFS 51.7% Pts treated prior to 1977 without doxorubicin based chemotherapy, or i.t. prophylaxis 5-y OS 15.4% 5-y PFS 15.4%
Deng et al., 2016 [36]	280	65 (10–96)	77	Anthracycline-containing regimen CHT (CHOP/CHOP-like regimen) 223 pts (91%) Rituximab treatment 161 pts (64%) Prophylactic i.t. 83 pts (34%) CHT + RT + i.t. prophylaxis 56 pts (24%)	Prophylactic RT to contralateral testis 96 pts (39%)	95% CR	212 pts (30%) 5-y/10-y cumulative risk of relapse: CNS 15%/21%, contralateral testis 6%/21% 10-y cumulative risk: EN 46% vs. ND 15% CNS and contralateral testis most common sites of relapse	5-y/10-y OS 58%/24% 5-y/10-y PFS 46%/38% 5-y/10-y DSS 66%/58% 5-y OS Age ≤60 vs. age >60 65% vs. 52%
Fonesca et al., 2000 [15]	62	68	79	CHT 22 pts (37%) CHT + RT 10 pts (16%) MTX i.t. × 4	RT 10 pts (16%)	ND	CNS 13 pts 80%	Median DFS/OS 2.7-y

*No relapses in contralateral testis; auto-SCT — autologous stem cell transplantation; CHOP-R-21 cyclophosphamide, doxorubicin, vincristine and rituximab on day 1, and prednisolone on days 1–5, administered every 21 days for a total of eight cycles; CHT — chemotherapy; CNS — central nervous system; COEP-R-14 — cyclophosphamide, vincristine, etoposide and rituximab on day 1, and prednisolone on days 1–5, administered every 14 days; CR — complete remission; CVP — cyclophosphamide, vincristine, etoposide and rituximab on day 1, and prednisolone on days 1–5; DFS — disease-free survival; DSS — disease-specific survival; EN — extranodal; FU — follow-up; GOELAMS — *Groupe Ouest Est d'Etude des Leucemies Aigues et Maladies du Sang*; i.t. — intrathecal; IELSG — International Extranodal Lymphoma Study Group; LN — lymph nodes; MACOP-B — methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; mo — month; MTX — methotrexate; ND — no data; OS — overall survival; PFS — progression-free survival; proMACE/cytaBOM — prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine; pts — patients; RT — radiotherapy; VCAP — vindesine, doxorubicin, cyclophosphamide, prednisolone; VECP-bleo — vindesine, epirubicin, cyclophosphamide, prednisolone, bleomycin

neither evidence of late neurological or cardiac toxicity nor of treatment-related mortality were observed [23]. Contradicting the abovementioned studies, a large retrospective analysis including 280 patients revealed no impact of i.t. prophylaxis on CNS relapse [37]. Our patients were treated with six courses of CHOP-R-21 immunochemotherapy, in 83% combined with i.t. prophylaxis with MTX and arabinoside cytosine, all resulting in durable complete remission. To date, scrotal RT has been performed in only one patient. Unfortunately, one patient who did not receive RT experienced relapse in the contralateral testis 72 months after treatment completion. After retreatment, he received the second CR and remains without signs of active disease after 63 months of further follow-up. This is very unusual, because the prognosis is poor in such cases and median survival in general does not exceed two months [38]. The National Comprehensive Cancer Network (NCCN) guidelines recommend 25–30 Gy RT to the contralateral testis as part of the treatment for PTL of any stage [38, 39]. Despite its benefit being supported by the results of retrospective and prospective trials, only 20–84% of PTL patients in 'real-world' analysis receive RT, although today this percentage is higher than it used to be [1, 2, 21, 37, 40, 41].

Adjuvant scrotal/contralateral testis RT has been found to decrease the risk of contralateral testis relapse and to prolong both OS and PFS [1, 2, 21, 37]. In a large retrospective analysis among PTL patients treated between 2004 and 2015, 49.8% of them received RT with a median dose of RT of 30 Gy, including 77% who received 30–39.9 Gy delivered over a median 16 treatments. The authors underscored that although RT requires multiple daily visits (delaying return to work), and may incur high out-of-pocket costs, it should never be omitted, especially in older patients with comorbidities, as these groups may be the least likely to tolerate aggressive salvage therapies at relapse [42].

All our patients remain in CR, although under strict observation, because very late relapses may occur. To conclude, even given all the limitations mentioned above, according to the available literature data it seems that the current standard treatment of PTL patients should include six courses of R-CHOP-21 with intrathecal MTX and scrotal adjuvant RT. Randomized, or even new, prospective studies are expected.

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Authors' contributions
MJ — concept, data collection and analysis, drafting article. LG — critical revision and approval of article. PC, ED — data collection and analysis. JRM — data analysis and critical revision of article. LG, KL — critical revision and approval of article.

Conflict of interest
The authors declare no conflict of interest.

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Ethics
The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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